Docket No.: 463-US-PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Benny Bang-Andersen, et al.
Application No.:	10/568,292
Filed:	August 14, 2006
Group Art Unit:	1624
Examiner:	Emily B. Bernhardt
Confirmation No.	3519
For:	TRANS-1-(6-CHLORO-3-PHENYLINDAN-1-YL)-3,3-DIMETHYLPIPERAZINE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

November 13, 2008

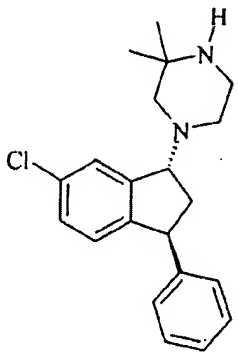
Sir:

DECLARATION OF **BENNY BANG –ANDERSEN** UNDER 37 C.F.R. 1.132

I, Benny Bang-Andersen, hereby declare as follows:

1. Klaus Peter Bøgesø, Henrik Svane, Lars Ole Lyngsø, Allan Carsten Dahl, Mark Howells, Klaus Gjervig Jensen, Tomas Mow and I conceived of, and reduced to practice, the invention claimed in the above-identified patent application, as to which we have been named co-inventors.

2. I have reviewed the above-identified patent application, which provides that the invention includes a compound, *trans*-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine of formula (I):



(I);

or a pharmaceutically acceptable salt thereof (hereinafter referred to as "Compound I").

3. I have reviewed the Office Action mailed May 13 2008, in connection with the above-identified patent application, along with the pending claims for the application and amended claims being submitted in response to the Office Action.

4. My co-inventors and I have found that Compound I of the invention is a relatively weak inhibitor of CYP2D6 in comparison to structurally related compounds (hereinafter referred to as, Compounds A-H). *See also e.g.*, paragraph **[0010]** of the published above-identified patent application (US 2006/0281758) (hereinafter, "the '758 published patent application").

5. CYP2D6 refers to Cytochrome P450 2D6, a mammalian enzyme that is commonly associated with the metabolism of around 30% of pharmaceutical compounds. Inhibition of this drug metabolizing enzyme may lead to clinically significant drug-drug interactions *i.e.*, if two drugs are given in combination and are metabolized by the same enzymes, competition for metabolism may give rise to increased plasma concentrations and therefore possible adverse effects. *See also, e.g.*, paragraphs **[0011]-[0012]** of the '758 published patent application.

6. The fact that Compound I has a low interaction with the liver enzyme CYP2D6 means that it has a reduced potential for drug to drug interaction, *i.e.*, the possibility for drug to drug interaction is less when a patient is treated with Compound I together with other drugs that are mainly metabolised by the CYP2D6 enzyme. This is a considerable advantage, in particular for

patients with schizophrenia, who are often treated with other medicaments to control their disease. *See also, e.g.,* paragraph **[0013]** of the '758 published patent application.

7. Experiments were conducted in the laboratory at H. Lundbeck A/S, Valby, Denmark, to determine the *in vitro* CYP2D6 inhibitory activity of Compounds A-I. The experiments were performed as described in the specification of the present invention, *e.g.,* at paragraphs **[0089]**-**[0090]** of the '758 published patent application.

8. As part of these experiments, Compound I was tested twice (batch 1 and batch 2), months apart, on August 30, 2002, and February 20, 2003, respectively, while Compounds A and C-F were tested between July 24, 2001 and June 3, 2003, Compound B was tested on December 20, 2006, and Compound H was tested on October 25, 2004.

9. Attached hereto as **Exhibit A** are tabulated results of the CYP2D6 experiments described in Points 7 and 8, above, along with the dates of testing.

10. The above-identified patent application also discloses that Compound I of the invention exhibits an IC_{50} higher than 5 μM for CYP2D6 activity. *See e.g.,* paragraph **[0089]** of the '758 published patent application.

11. As a general Rule of Thumb for IC_{50}: a potent inhibitor has an $IC_{50} < 0.5$ μM, a moderate inhibitor has an $0.5\ \mu M < IC_{50} < 5\ \mu M$ and a weak inhibitor has an $IC_{50} > 5$ μM. These classifications may be raised if the plasma concentration to the supposed drug is higher than "average" or lowered if only a trace amount is needed.

12. As seen from **Exhibit A**, Compound I exhibits an $IC_{50} > 5$ μM for CYP2D6 activity; and therefore, is a weak inhibitor of CYP2D6.

13. As seen from **Exhibit A**, Compounds A-E exhibit an $IC_{50} < 0.5$ μM for CYP2D6 activity; and therefore are potent inhibitors of CYP2D6.

14. As seen from **Exhibit A**, Compounds F and H exhibit an IC_{50} of 1.3 μM and 2.7 μM, respectively, for CYP2D6 activity; and therefore are moderate inhibitors of CYP2D6.

15. As seen from **Exhibit A**, Compound G exhibits an IC_{50} of > 5 μM for CYP2D6 activity; and therefore is a weak inhibitor of CYP2D6.

16. It is noted that the prior art patent, EP 0 638 073 B1 ("EP'073") generically discloses Compounds A-H, *e.g.*, with respect to formula I, paragraph **[0002]**. It is also noted that EP'073 specifically discloses Compound C as the 1.5 maleate salt (*e.g.*, at page 9, lines 6-7 (Compd. 10)), and Compound H as the hemifumarate salt *(e.g.*, Example 2).

17. It is noted that the prior art reference, Bøgesø et al., *J. Med. Chem.* 1995, 38:4380-4392 ("the Bøgesø reference") generally disclose Compounds A-H and specifically discloses Compounds A-C and F-H (*see e.g.*, Figure 1 and Table 5, compounds A-C: (-)-38, (+)-38, and 38 , and compounds F-H: (-)-41, (+)-41 and 41).

18. It is apparent from the results presented in **Exhibit A** that the inhibitory activity of Compound I of the present invention towards CYP2D6 is significantly lower than for the structurally related Compounds A-F, and H.

19. Although Compound I does not have an inhibitory activity towards CYP2D6 lower than that of Compound G, it was unpredictable, surprising and unexpected that the CYP2D6 inhibitory activity of Compound I was significantly lower than that of the other structurally related Compounds A-F, and H, and that it is a weak inhibitor of CYP2D6 activity compared to them.

20. It was surprising, unexpected and unpredictable as stated in Point 19, above, because, for example:

    a. in view of Compounds A-C (the two enantiomers and racemate of *trans*- 4-(6-chloro-3-phenyl-2,3-dihydro-1H-inden-1-yl)-1,2,2-trimethylpiperazines) all exhibiting an IC_{50} less than 0.5 μM, and thus all being potent inhibitors of CYP2D6, it was surprising and unexpected to find that Compound I is a weak inhibitor of CYP2D6 activity when its enantiomer (Compound D) and the racemate of it and Compound D (Compound E) both exhibit an IC_{50} less than 0.5 μM, and thus, are both potent inhibitors of CYP2D6;

b. in viewing the CYP2D6 inhibitory activity of the Compounds, *e.g.*, by the potency ratio of each group of derivatives, where the potency ratio is the IC_{50} of the least potent Compound to the IC_{50} of the racemate Compound, it was surprising and unexpected to find that the potency ratio of Compound I to Compound E was significantly greater than the potency ratios for Compound C to Compound A (C:A) and Compound H to Compound G (H:G). Where the C:A potency ratio and the H:G potency ratio are 3.3, the potency ratio of Compound I to Compound E (I:E) is 108; and, the I:E potency ratio of 108 is based on the lower of the two IC_{50} values for Compound I. Attached hereto as **Exhibit B** are the calculations for the C:A, H:G and I:H potency ratios; and

c. in view of this, it also was unpredictable whether Compound I would be a potent, moderate or weak inhibitor of CYP2D6.

21. Also, because Compound I is a weak inhibitor of CYP2D6 activity, it is anticipated that it will have a reduced potential for drug to drug interaction when given in combination with another drug that is mainly metabolized by the CYP2D6 enzyme, such as, *e.g.*, haloperidol and/or risperidone. This is expected to be advantageous for the patient, such as a schizophrenic patient, who often is on more than one drug therapy.

22. Thus, Compound I claimed in the above-identified patent application possesses surprising, unexpected and unpredictable properties over the prior art Compounds A-H.

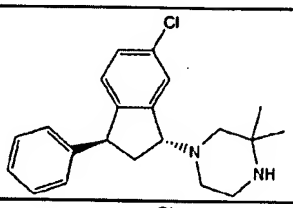
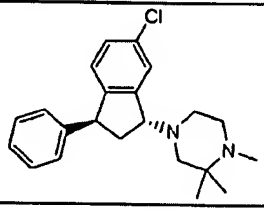
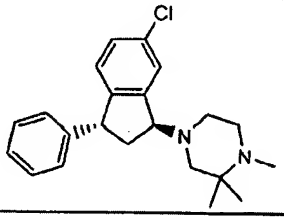
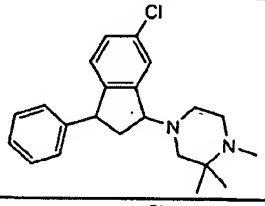
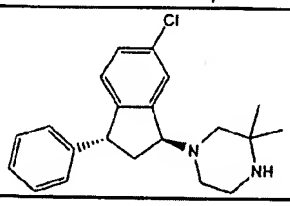
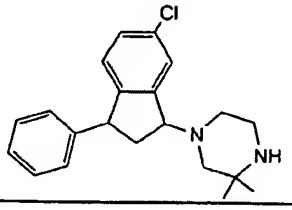
23. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

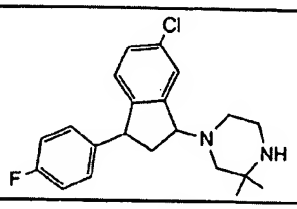
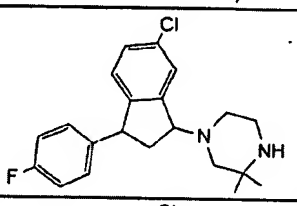
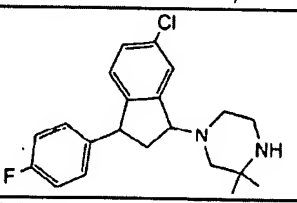
13 November 2008

Date

Benny Bang-Andersen

Exhibit A

Compound ID	Compound Structure	Compound Name	CYP2D6 IC_{50} (μM)	Test Date
Compound I		*trans*-1-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine) (enantiomer of Cpd E)	7.9*; 5.4**	30-Aug-02* 20-Feb-03**
Compound A		*trans*-4-((*1R,3S*)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (enantiomer of Cpd C)	0.1	20-Jul-01
Compound B		*trans* -4-((*1S,3R*)-6-chloro-3-phenyl-2,3-dihydro-1H-inden-1-yl)-1,2,2-trimethylpiperazine (enantiomer of Cpd C)	<0.02	20-Dec-06
Compound C		(±)-*trans*-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (racemate of Cpds A & B)	0.03	24-Aug-01
Compound D		*trans*-1-((*1S,3R*)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd E)	0.2	3-Jun-03
Compound E		(±)-*trans*-1-(6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (racemate of Cpds I & D)	<0.05	24-Jul-01

Compound ID	Compound Structure	Compound Name	CYP2D6 IC_{50} (μM)	Test Date
Compound F		*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine (enantiomer of Cpd H)	1.3	3-Feb-03
Compound G		*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3.3-dimethylpiperazine (enantiomer of Cpd H)	9	7-Aug-02
Compound H		(±)-*trans*-1-(6-chloro-3-(4-fluorophenyl)-indan-1-yl)-3,3-dimethylpiperazine (racemate of Cpds F & G)	2.7	25-Oct-04

*batch 1; **batch 2

Appendix B

$$\text{Potency Ratio for CYP2D6 inhibitory activity of a group of derivatives} = \frac{IC_{50} \text{ of the least potent Compound}}{IC_{50} \text{ of the racemate Compound}}$$

A:C Compounds Potency Ratio = 0.1 / 0.03 = 3.3

H:G Compounds Potency Ratio = 9 / 2.7 = 3.3

E:I Compounds Potency Ratio = 5.4[†] / 0.05 = 108

[†]The lower of the two IC_{50} values for Compound I.